787FM.2.1 AZATHIOPRINE FOR USE IN RHEUMATOLOGY, DERMATOLOGY, GASTROENTEROLOGY AND RESPIRATORY MEDICINE
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for azathioprine therapy. It should be read in conjunction with the shared care responsibilities document, the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

BACKGROUND FOR USE

- Azathioprine is an immunosuppressant. It is licensed for use alone or with other agents to enhance the survival of organ transplant patients.
- It is used as a disease modifying anti-rheumatic drug (DMARD) and as a steroid-sparing agent.
- Indications, dose adjustments and monitoring requirements for DMARDs (licensed and unlicensed indications) defined in the Buckinghamshire shared care protocols are in line with national guidance published by the British Society for Rheumatology, the British Association of Dermatologists, the British Society of Gastroenterology and British Thoracic Society.
- Azathioprine uses in this protocol are limited to:

Rheumatology
- Severe rheumatoid arthritis, dermatomyositis, systemic lupus erythematosus (SLE) (licensed).
- Other autoimmune rheumatic diseases (ARD) including polymyositis and systemic vasculitis. Use in systemic vasculitis *is unlicensed and recommended by the British Society of Rheumatology.*[1]

Dermatology
- Pemphigus vulgaris (licensed).
- Atopic eczema, bullous pemphigoid, pyoderma gangrenosum, chronic actinic dermatitis and cutaneous vasculitis. Use in these conditions is unlicensed and recommended by the British Association of Dermatologists.

Gastroenterology
- Inflammatory bowel disease (licensed).
- Autoimmune liver disease, IgG4 disease (unlicensed) and recommended by the British Society of Gastroenterology.[2]

Respiratory Medicine
- Interstitial lung disease (unlicensed). Its use in this condition is recommended by the British Thoracic Society.[3]

SUPPORTING INFORMATION

Azathioprine is an established drug with a known side effect profile.

CONTRAINDICATIONS

- Hypersensitivity to 6-mercaptopurine or azathioprine
- Severe infections
- Severe hepatic/renal impairment
- Pancreatitis
- Absent or very low homozygous thiopurine methyl transferase (TMPT) levels.

RELATIVE CONTRAINDICATIONS

- Low heterozygous TPMT levels (lower doses should be used)

PRECAUTIONS

Immunisation with LIVE vaccines	Patients receiving azathioprine must NOT receive immunisation with LIVE vaccines. Inactivated polio is available although sub-optimal response may be seen.
Chickenpox/ shingles	Stop azathioprine if proven infection. For those with exposure to chickenpox or shingles and no history of infection/vaccination, check that immunity to Varicella zoster virus (VZV) infection has been checked. If the patient is susceptible, a course of oral aciclovir or valaciclovir is recommended unless there are significant concerns of renal toxicity or malabsorption. Discuss with a Microbiologist.
Pregnancy and breastfeeding	Azathioprine is compatible throughout pregnancy at ≤2 mg/kg/day[1]. Azathioprine is also compatible in breastfeeding and paternal exposure.
Renal impairment Hepatic impairment	Dose reduction necessary.

DOSAGE

Indication	Dose	Ref
Severe rheumatoid arthritis and other ARDs	Up to 1 mg/kg daily increasing after 4 to 6 weeks to 2 to 3 mg/kg daily. The maintenance dose may be 1 to 3 mg/kg daily. Usual dose range 50 – 250 mg daily.	1
Dermatological conditions	Usual maintenance dose of 1 mg to 3 mg/kg daily. Usual dose range 50 - 250 mg daily.	
Inflammatory bowel disease	Usual maintenance dose of 2 to 2.5 mg/kg daily. Some patients respond to lower doses. Usual dose range 100 – 250 mg daily.	2
Interstitial lung disease	Usual maintenance dose 2 mg/kg daily. Initially 50 mg daily. Increase dose by 50 mg each month up to a maximum of 150 mg daily. Usual dose range 50 – 150 mg daily.	3

Prescribing points

Prescriptions must state the form, strength, dose and directions in full.

The use of 'as directed' in prescribing should be avoided. A specific dose must be applied to each prescription.

TIME TO RESPONSE

Six weeks to three months.[1]

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

- Weight, height and blood pressure where relevant to speciality.
- Full blood count (FBC), urea and electrolytes (U&E), creatinine, albumin, alanine transaminase (ALT), erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).
- TPMT genotype should be checked. TPMT is a key enzyme in azathioprine metabolism which is inherited in an autosomal dominant pattern. Up to 12% of the population has reduced or very low TPMT activity and these individuals can be very sensitive to standard doses of azathioprine.
- Offer testing for hepatitis B, C and human immunodeficiency virus (HIV) serology in particular if patient is at risk of occult viral infection.
- Check VZV serology (if no history of varicella). The specialist should give advice about treatment required if there is exposure to or new diagnosis of chickenpox or shingles.

VACCINATION

Pneumococcal vaccination should be administered as a single dose polysaccharide PPV-23 (Pneumovax®), if possible, prior to initiation of azathioprine therapy or as soon as possible after.

Annual influenza vaccine should be recommended to all patients.

ROLES AND RESPONSIBILITIES

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Unless otherwise stated in the protocol, the responsibilities are as follows:

Specialist

- Initiate treatment and prescribe until the dose is stable and/or the GP formally agrees to shared care.
- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Provide copy of patient information leaflet and drug monitoring card where appropriate.
- Send a letter to the GP requesting shared care. Outline shared care protocol criteria and how often monitoring should be done.
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments.
- Be available to give advice to GP and patient throughout treatment.

GP

- Prescribe medication once the dose is stable and shared care is agreed.
- Ensure all monitoring is completed in accordance to the specific shared care protocol.
- Check and record results then advise the specialist of any deteriorations or abnormal results.
- Notify the specialist to any changes in patient's condition, any adverse drug reactions or failure to attend tests.

Patient

- Agree to treatment and monitoring after making an informed decision.
- Agree to being under the shared care of the GP and specialist.
- Attend for blood tests and monitoring when required.
- Ensure monitoring card is kept up to date and is brought to all appointments.
- Report any side effects to the GP or a member of the specialist team.

Note: If the patient does not attend blood monitoring, then treatment will be stopped. If the patient is more than 4 weeks late with their monitoring, then treatment should be stopped.

ONGOING MONITORING SCHEDULE

Rheumatology, and respiratory indications	**Initiation:** FBC, creatinine, estimated glomerular filtration rate (eGFR), albumin and ALT every 2 weeks until on stable dose for 6 weeks. **Stable dose:** Monthly FBC, creatinine, eGFR, albumin and ALT for 3 months; and thereafter, FBC, U&E, albumin and ALT at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity. The specialist will advise if this is necessary. **Dose increase**: FBC, creatinine, eGFR, albumin and ALT every 2 weeks until on stable dose for 6 weeks, then revert back to previous schedule. This will be initiated by the specialist. ESR or CRP: 1 to 3 monthly as advised by the specialist.
Gastroenterology indications	**Initiation:** FBC, creatinine, eGFR, albumin and ALT every 2 weeks until on stable dose for 6 weeks. **Stable dose:** Monthly FBC, creatinine, eGFR, albumin and ALT for 3 months; and thereafter, FBC, creatinine, eGFR, albumin and ALT at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity. The specialist will advise if this is necessary. **Dose increase**: FBC, creatinine, eGFR, albumin and ALT every 2 weeks until on stable dose for 6 weeks, then revert back to previous schedule. This will be initiated by the specialist. ESR or CRP: 1 to 3 monthly as advised by the specialist.

Dermatology	**Initiation:** FBC, albumin, ALT, creatinine and eGFR weekly for 4 weeks, then every 2 weeks for 4 weeks. **Stable dose:** Monthly FBC, albumin, ALT, creatinine and eGFR for 3 months, then at least every 12 weeks. More frequent monitoring in patients at higher risk of toxicity. The specialist will advise if this is necessary. **Dose increase**: FBC, albumin, ALT, creatinine, eGFR weekly for 4 weeks, then every 2 weeks for 4 weeks, then monthly for 3 months, then revert back to previous schedule. This will be initiated by the specialist.

In addition to absolute values for haematological indices, a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance. In order to monitor trends it is recommended that all blood test results are entered in the patient held monitoring booklet.

SIDE EFFECTS AND ACTIONS TO BE TAKEN

Side Effects	Action
White blood cell count (WBC) $<3.5 \times 10^9$/l Neutrophils $<1.6 \times 10^9$/l Lymphocytes $<0.5 \times 10^9$/l	Withhold and discuss with a specialist.
Platelets $<140 \times 10^9$/l	Withhold and repeat. If low discuss with a specialist.
ALT >2 upper limit of normal reference range (or >100 units/l)	Withhold. Look for alternative cause. Repeat liver function tests (LFTs), if abnormal discuss with a specialist.
Mean cell volume (MCV) >105 fl	Check folate, B_{12} and thyroid function tests (TFTs), and treat if appropriate. If WBC normal repeat in 4 weeks. Folic acid should be given at a dose of 5 mg PO once daily and vitamin B_{12} is given as hydroxocobalamin injection 1 mg IM three times a week for 2 weeks, then 1 mg IM every three months.
Rash or oral ulceration	Withhold until symptoms clear. Consider re-challenging at a lower dose. If rash recurs stop azathioprine and discuss with a specialist. Treat oral ulceration.
Hypersensitivity reactions	Fever, malaise, rash, vomiting, muscle/bone pain, dizziness. Stop azathioprine. Hypersensitivity to mercaptopurine should alert the prescriber to a probable hypersensitivity to azathioprine.
Abnormal bruising or sore throat	Withhold until FBC result available.
Nausea, vomiting, diarrhoea	Usually resolves after a few weeks without alteration of dose. Administer tablets after meals to reduce nausea. An anti-emetic or dose reduction may help. If symptoms persist stop azathioprine.

- Azathioprine can be withheld for several days without causing a flare.
- Sunscreens and protective covering should be encouraged to reduce sunlight exposure.

NOTABLE DRUG INTERACTIONS (REFER TO BNF AND SPC)

- **Ribavirin: Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore co-administration is not advised.**
- **NSAIDs:** May be continued. Indometacin can increase the risk of myelosuppression and should be avoided.
- **Allopurinol/oxipurinol/thiopurinol:** The dose of azathioprine should be reduced to one quarter of the original dose.
- **Febuxostat:** Febuxostat is predicted to increase the exposure to azathioprine. Manufacturer advises avoid.
- **Warfarin:** Inhibition of the anticoagulant effect of warfarin has been reported. The INR should be monitored regularly.
- **Drugs which may have a myelosuppressive effect, e.g. penicillamine:** Where possible, avoid co-prescribing.

- **Aminosalicylate derivatives, e.g. mesalazine, sulfasalazine:** Should be administered with caution as can contribute to bone marrow toxicity.
- **Vaccines:** Atypical reactions to live vaccines could occur. They are contraindicated and should be avoided. A diminished response to inactivated vaccines can be expected.
- **Angiotensin-converting enzyme (ACE) inhibitors:** Co-prescription may cause anaemia and severe leucopenia.
- **Co-trimoxazole and trimethoprim:** Can cause life threatening haematotoxicity.
- **Neuromuscular agents** e.g succinylcholine. Patients should be informed to let the anaesthetist know that they are on azathioprine if they need surgery.

BACK-UP INFORMATION/ADVICE

Contact Details	Wycombe and Amersham	Stoke Mandeville
Dermatology	09:00 – 17:00 contact on-call registrar or consultant via switchboard 01494 526161	09:00 – 17:00 contact on-call registrar or consultant via switchboard 01296 315000
Rheumatology	01296 315960 (specialist nurse helpline – may take 48 hours for response; not for urgent queries) Secretaries Office: 01494 734079 In an emergency contact Consultant Rheumatologist on-call via switchboard 01296 315000 Email: bht.rheumatology@nhs.net	01296 315960 (specialist nurse helpline – may take 48 hours for response; not for urgent queries) In an emergency contact consultant rheumatologist of the week 01296 316664 Rheumatology Reg: Bleep 905/907 via switchboard. Email: bht.rheumatology@nhs.net
Respiratory Medicine		Chest Office: 01296 315686 / 315687
Gastroenterology	Registrar bleep 543 via switchboard Consultant secretary: Dr Cullen 01494 425267 Dr Gorard 01494 425267 Dr Johns 01494 425595 Dr Maggs 01494 425595	Registrar bleep 894 via switchboard Consultant secretary: Dr Sekhar 01296 316865 Dr Hossein 01296-316974
Medicines Resource Centre	01494 425355	

SHARED CARE AGREEMENT FORM

Available on DocGen. When not available, use the Word version linked here.

REFERENCES

1. Leadingham J et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology 2017; 56(6); 865–868 https://academic.oup.com/rheumatology/article/56/6/865/3053478
2. Carter MJ, Lobo AJ and Travis SPL on behalf of the IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004; 53(Suppl V); v1-v16.
3. British Thoracic Society. Interstitial Lung Disease Guidelines https://www.brit-thoracic.org.uk/document-library/guidelines/interstitial-lung-disease/bts-guideline-for-interstitial-lung-disease/
4. Meggitt et al. British Association of Dermatologists' guideline for the safe and effective prescribing of azathioprine 2011. British Journal of Dermatology 2011;165:711-734.
5. NICE May 2019. Ulcerative colitis: management [CG130] https://www.nice.org.uk/guidance/ng130
6. NICE May 2019. Crohn's disease: management [CG129] https://www.nice.org.uk/guidance/ng129

See also:
Guideline 280FM Management of Patients on Immunosuppressants admitted with Suspected Infections

Title of Guideline	Azathioprine for Use in Rheumatology, Dermatology, Gastroenterology and Respiratory Medicine
Guideline Number	787FM
Version	2.1
Effective Date	December 2019
Review Date	December 2022
Amended	September 2020
Original Version Produced	February 2011
Approvals:	
Medicines Value Group	22nd September 2019
Clinical Guidelines Subgroup	5th November 2019
Author/s	Dr M Magliano, Dr J Chana, Rheumatology consultants Dr F Hossein, Gastroenterology consultant, Dr Amal Eissa, Dermatology consultant, Dr C Wathen, Respiratory consultant, Breda Cronnolly, Interface Pharmacist
SDU(s)/Department(s) responsible for updating the guideline	Rheumatology, Dermatology, Gastroenterology, Respiratory Medicine
Uploaded to Intranet	11th December 2019 and 15th September 2020
Buckinghamshire Healthcare NHS Trust/NHS Buckinghamshire Clinical Commissioning Group.	